REMARKS

In the present amendment, claims 1, 2, 4, 5, 7, 9, 12-13, 15-20, 22, 24-25, and 27-31 are amended, claims 3, 6, 14, 21, and 23 are canceled; claim 32 was previously canceled, claims 8, 10, and 11 are original claims and claims 26 and 33 were previously presented. Support for the amendments can be found throughout the specification, including the claims as filed. The GM-CSF-encoding DNA of the amended claims provides a means for modulating the host's immune response to augment the therapeutic effectiveness of the recombinant viruses defined by the claims. *See* page 8, lines 17-21. Applicant reserves the right to pursue the subject matter of the previously presented claims in future prosecution. Claims 1-2, 4-5, 7-13, 15-20, 22, 24-31 and 33 are currently pending.

I. Outstanding Rejections

Claims 1-31 and 33 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly not enabled by the specification

II. Patentability Arguments

A. The Enablement Rejection

Claims 1-31 and 33 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly not enabled by the specification. Although the Examiner acknowledged that the application enabled methods of treating neoplastic disease of the CNS comprising administration of herpes simplex virus therapeutics incapable of expressing $\gamma_1$34.5 and expressing IL-4, the Examiner asserted that methods of treating with a cytokine other than IL-4 were not enabled. Additionally, the Examiner asserted lack of enabling support for (1) making HSVs expressing only one $\gamma_1$34.5, (2) treating any neoplastic disease using such HSVs, and (3) treating neoplastic disease with any encoded cytokine. In response, Applicants note that the present amendment renders moot the rejection of claims 1-31 and 33 under § 112, first paragraph, and a corresponding rejection of the claims as amended would be improper for the reasons provided below.

The pending claims as amended herein are drawn to HSV therapeutics that are incapable of expressing $\gamma_1$34.5 and that are capable of expressing GM-CSF. Enabling support for the subject matter of the amended claims is found throughout the application as filed. The Examiner acknowledges that the application contains disclosure relating to an HSV that is incapable of expressing $\gamma_1$34.5 because each of the copies of that gene in the

HSV genome has been rendered incapable of expressing an active gene product. Moreover, a modified HSV of the claims is defined as being capable of expressing GM-CSF, a particular cytokine, rather than any cytokine. With respect to the diseases amenable to treatment, Applicants initially note that claims 1-18 are drawn to a recombinant HSV and not to a method of treatment; accordingly, this basis for rejecting claims 1-18 is inappropriate. Claims 19-31, drawn to methods of treating neoplastic disease, do not recite the treatment of any disease but, rather, neoplastic disease.

Within the group of neoplastic diseases, use of a recombinant HSV capable of expressing GM-CSF is fully enabled. The Examiner cited two references of record to show that GM-CSF may not be useful in generating an anti-tumor immune response. Those two references, Bronte et al., J. Immunol. 154:5286-5292 (1995) ("Bronte") and Irvine et al., J. Immunol. 156:238-245 (1996) ("Irvine") do not stand for the propositions put forth by the Examiner at page 9 of the Office Action. The Examiner characterized Bronte as demonstrating that "recombinant virus encoding GM-CSF . . . does not result in the inhibition of pulmonary metastases," citing page 5287 and Fig. 4. In the legend to Fig. 4 of Bronte, however, the authors state that "[a] drVV [double-recombinant vaccinia virus] expressing IL-2, but not GM-CSF . . . significantly reduces the number of pulmonary metastases in a 3-day model." That statement, and the data shown in Fig. 4, may establish that a vaccinia virus expressing a tumor antigen and IL-2 more significantly reduces pulmonary metastases than a vaccinia virus expressing a tumor antigen and GM-CSF. A less significant reduction of pulmonary metastases attributable to vaccinia virus expressing a tumor antigen and GM-CSF, however, does not mean that the GM-CSF-expressing vaccinia virus failed to result in any reduction of pulmonary metastases, or even failed to result in a significant reduction of pulmonary metastases. At page 5285 of Bronte, in fact, the authors expressly state that "[a] partial decrease [in the number of pulmonary nodules] was obtained with the other cytokine-encoding viruses and with VJS6." The "other cytokine-encoding viruses" included the GM-CSF-encoding virus. Thus, Bronte does not teach that a combination therapy, in which vaccinia virus delivers tumor antigen and GM-CSF, failed to reduce pulmonary tumor nodules. Whether that therapy worked as well as vaccinia virus delivering tumor antigen and IL-2 is not probative on the present enablement issue.

The Examiner characterized Irvine as teaching that "the administration of . . . GM-CSF . . . do[es] not induce antigen specific immunotherapy of tumors in vivo in

immunocompetent mice," citing page 241, col. 2, paragraph 1 and page 243, col. 1. The first of the Examiner's cited passages states that "GM-CSF promotes the differentiation of hematopoietic precursors to dendritic cells that function to present Ag [antigen] to prime naïve lymphocytes." Further, that passage discloses that mice were immunized with a plasmid encoding β-gal as a tumor antigen and treated some hours later with any of a variety of cytokines, including GM-CSF. Only some of those cytokines, not including GM-CSF, "were found to specifically induce Ag-specific active immunotherapy." The reported result, which was not shown, is hardly surprising in view of the knowledge in the art regarding GM-CSF that was expressly stated in Irvine. GM-CSF was known to promote development of APCs or antigen-presenting cells. As Irvine itself expressly stated in the second passage cited by the Examiner (page 243), "[t]he findings in this study, that GM-CSF did not act as an adjuvant, suggested that the APC are not limiting when the Ag is supplied by DNA immunization." Importantly, Irvine did not state that a combination therapy involving a DNA vaccine and GM-CSF was inoperative; rather, it states that the GM-CSF did not detectably contribute to the therapeutic effect. Such an outcome would have been expected by one of skill in the art, given the knowledge that GM-CSF promotes development of antigen-presenting cells and the DNA vaccine is already providing ample antigen to ensure adequate presentation, as effectively acknowledged by the authors. Thus, the results reported in Irvine are not unpredictable and Irvine does not stand for the proposition that treatments of neoplastic disease comprising delivery of GM-CSF are unpredictable. Additionally, the claimed methods do not involve the enhanced delivery of a tumor antigen and would not be expected to lead to the same result as reported in Irvine. Thus, Irvine does not establish that the claimed method of treating neoplastic disease comprising delivery of GM-CSF is unpredictable, Irvine does not disclose that any method of treating a cancer with GM-CSF is inoperative, and there is no reasonable basis for believing that the claimed methods would lead to Irvine's result, even if Irvine could be construed as disclosing an inoperative method.

For the foregoing reasons, Applicants submit that the Examiner's basis for rejecting the claims as lacking enablement is flawed, and reliance on that basis in rejecting any of the claims as amended would be misplaced. Beyond addressing the Examiner's position, however, Applicants submit that a consideration of the Wands factors leads to the conclusion that the claimed subject matters, both recombinant HSVs and methods of treating neoplastic disease, are enabled.

Applicants submit that a consideration of the Wands factors leads to a conclusion that the claims as amended are enabled throughout their full scopes by the application as filed. The predictability factor has been considered above in the context of addressing the Examiner's position and, given the extensive knowledge regarding HSV biology and the knowledge concerning GM-CSF, a consideration of this factor favors a finding that the claims are enabled throughout their full scopes.

As for guidance, the Application teaches modification of $\gamma_1$34.5 such that the two $\gamma_1$34.5 genes are incapable of expression and the Examiner has not challenged that teaching. Moreover, the Application teaches that such modified HSV are useful for treating neoplastic disease, in conjunction with a cytokine, such as GM-CSF. Dosaging and routes of administering such therapeutics will vary for each application, and are determinable using routine procedures, as was known in the art. Accordingly, the application as filed provides ample guidance in making and using the claimed subject matter.

The nature of the invention, treatment methods for known and relatively well-characterized neoplastic diseases using a modified form of a well-characterized virus, HSV, also favors a conclusion that the pending claims are enabled by the application as filed. Those of skill in the field of medicine are well-versed in treatments for neoplastic diseases and in the administration of biologics. Thus, the nature of the invention favors enablement and, at a safe minimum, cannot be a significant factor in any fair conclusion that the claims are not enabled throughout their full scopes. Two related factors, the state of the art and the level of skill in the art, also favor a conclusion that the claims are enabled. The Examiner has cited references which, collectively, establish that the state of the relevant art was advanced, and medical practitioners are widely recognized as being highly educated and possessing a high level of skill.

With respect to the presence or absence of working examples, that factor alone is not dispositive on the issue of enablement. Moreover, the examples provided in the application as filed include the use of recombinant HSV modified such that they are incapable of expressing $\gamma_1$34.5. Consequently, this factor also favors a finding that the full scopes of the claims as amended are enabled. As for the quantity of experimentation necessary, routine experimentation to optimize administration of the therapeutic is

insignificant. Any additional experimentation that may be necessary to determine the suitability of practicing the claimed methods in a particular context would involve a straightforward assessment by *in vitro*, *ex vivo* or animal-based *in vivo* assay. Given the highly developed state of the art and the high level of skill in that art, any of a number of such straightforward assays may be identified as suitable under a given set of circumstances. Rare experimentation in the form of conducting a simple assay where indicated, coupled to routine experimentation to optimize delivery, does not signal a significant quantity of required experimentation. Finally, the pending claims are precisely tailored to the invention disclosed in the application – the recombinant HSVs comprising modifications rendering the HSVs incapable of expressing $\gamma_1$34.5 but capable of expressing GM-CSF, and the use of such HSVs in methods for treating neoplastic diseases. Thus, the breadth of the claims is a factor also favoring a determination that the pending claims are enabled throughout their full scopes by the application as filed.

In view of a consideration of all of the factors relevant to an enablement inquiry and in view of the flawed basis for the Examiner's position on the issue, Applicants submit that the Examiner cannot establish a *prima facie* case of non-enablement for the subject matter of any of the claims as amended and, for that reason, imposing a rejection of any of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement would be improper.

B. Art-based rejections

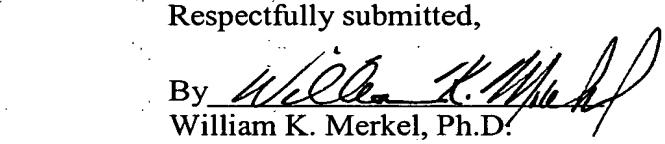
The Office Action, mailed March 30, 2005, indicated that there were no outstanding art-based rejections. Applicants submit that while art-based rejections had been imposed against prior claims drawn to HSVs incapable of expressing $\gamma_1$34.5, those prior claims were also drawn to HSVs capable of expressing a cytokine, not the GM-CSF recited with particularity in the claims as amended. Any art-based rejection that fails to disclose or suggest each limitation of the claims as amended herein is defective and would be improper.

Conclusion

In view of the above amendments and remarks, Applicants submit that each of the outstanding rejections of the claims has been overcome and the claims are now in condition for allowance.

Dated: August 30, 2005

Respectfully submitted,

By 

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